CONCISE REPORT

New onset or exacerbation of psoriatic skin lesions in patients with definite rheumatoid arthritis receiving tumour necrosis factor α antagonists

S Kary*, M Worm*, H Audring, D Huscher, M Renelt, H Sörensen, E Ständer, U Maaß, H Lee, W Sterry, G-R Burmester

Ann Rheum Dis 2006;**65**:405–407. doi: 10.1136/ard.2005.037424

Background: Blockage of tumour necrosis factor α (TNFα) is highly effective in rheumatic diseases, especially in rheumatoid arthritis (RA), ankylosing spondylitis, and psoriatic arthritis. Furthermore, TNFα antagonists have also been shown to significantly reduce psoriatic skin lesions.
Case reports: A series of nine patients with RA who were treated with different types of TNFα antagonists and who unexpectedly developed either a new onset or an exacerbation of psoriatic skin lesions are reported

The selective inhibition of tumour necrosis factor α (TNFα) leads to significant improvement of disease activity in patients with immunologically mediated inflammation such as rheumatoid arthritis (RA), ankylosing spondylitis, Crohn's disease, and psoriatic arthritis. Two monoclonal antibodies, infliximab and adalimumab, and the receptor construct, etanercept, are available. These TNFα antagonists have also proved to be effective in psoriatic skin disease in clinical trials, and etanercept has been approved for this indication.[1–5]

CASE REPORTS

Case 1

A 41 year old woman with RA was treated in a clinical trial with adalimumab 40 mg subcutaneously weekly and after 9 months every other week. After 14 months' treatment she noticed about 10 small vesicles of 2 mm diameter on one ankle. During the following weeks, pruritus, pustules, scales, erythema appeared on palms and soles, both legs and arms, and the scalp. Psoriasis vulgaris was clinically (fig 1) and histologically (fig 2) diagnosed at the Department of Dermatology and Allergy, Charité University Medicine Berlin. Adalimumab was discontinued, but the psoriasis did not improve. Four months later, etanercept 25 mg twice weekly was started with an initially good effect on the RA and psoriasis, but a severe skin disorder recurred in the third week. A combination of etanercept and methotrexate (MTX) 15 mg/week orally, and topical treatment followed for 6 months, with moderate effect on the psoriasis. Owing to a temporary unavailability of etanercept, infliximab 100 mg per infusion was started, with almost complete remission of the psoriasis after the first administration. However, the psoriasis became severely exacerbated after the second infusion with the same dose. The patient herself discontinued all drugs for 1 year. Thereafter, the combination of etanercept and MTX was re-introduced because her RA was severely active. The psoriasis lesions remained, limited to palms and soles.

Case 2

A 69 year old woman with RA was treated with etanercept 25 mg twice weekly for 1 month. She experienced scales and pustules exclusively on palms and soles. Psoriasis palmoplantaris pustulosa was diagnosed at the Department of Dermatology and Allergy, Charité University Medicine Berlin. The patient had had a previously known underlying but inactive psoriasis for about 8 years. Etanercept was temporarily interrupted, and her skin lesions improved upon topical treatment. Currently, the patient is receiving etanercept (25 mg/week). Psoriatic lesions recur to a moderate extent about once a month.

Case 3

A 65 year old woman with RA received an injection of adalimumab 40 mg in combination with leflunomide (LEF) 20 mg/day. Four days after the first injection scaly lesions of 10 mm diameter appeared on the limbs. Psoriasis vulgaris was histologically diagnosed at the Department of Dermatology and Allergy, Charité University Medicine Berlin. Adalimumab was discontinued for 5 weeks. After improvement of the skin lesions, adalimumab was restarted, and the skin inflammation remained stable. The patient had formerly received etanercept 25 mg twice weekly during a clinical trial in 2001 for several months without occurrence of psoriatic skin lesions.

Case 4

A 38 year old man with RA received an injection of infliximab (3 mg/kg body weight) combined with LEF (20 mg/day). Three months after the first infusion he noticed scaly skin lesions with a diameter ranging from 2 mm to 20 mm on limbs and abdomen, but not on palms or soles. Psoriasis vulgaris was clinically confirmed by a dermatologist. Two months later, the anti-TNFα treatment was changed to etanercept 25 mg twice weekly because of insufficient antirheumatic effect. The psoriasis improved, but the response of RA was insufficient. Adalimumab 40 mg every other week was now applied with good effect on the RA, but after 6 weeks the psoriatic symptoms reappeared on both thighs. The patient's sister has psoriasis vulgaris.

Case 5

A 67 year old woman with RA was injected with adalimumab 40 mg every other week in combination with LEF 20 mg/day and MTX 15 mg/day. Five months after the first injection

*S Kary and M Worm contributed equally to this article.

Abbreviations: LEF, leflunomide; MTX, methotrexate; RA, rheumatoid arthritis; TNFα, tumour necrosis factor α

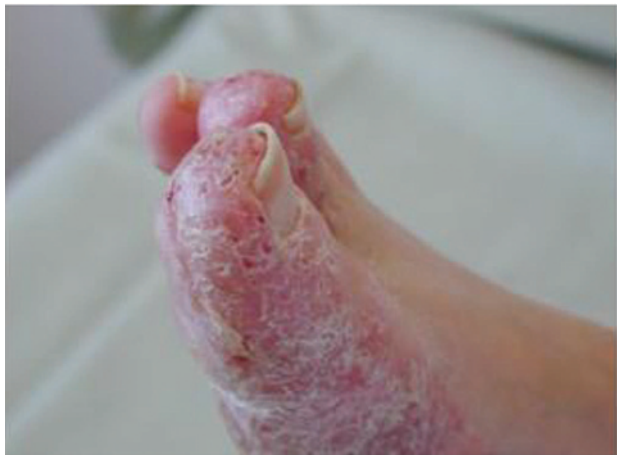

Figure 1 Psoriasis vulgaris (case 1).

about 10 scaly and erythematous lesions of up to 10 cm in diameter as well as some pustules on palms, arms, legs, and scalp appeared. Psoriasis pustulosa was clinically and histologically confirmed by a dermatologist. LEF was discontinued, but the skin lesions did not improve. A brother has psoriasis vulgaris.

Case 6

A 49 year old woman with RA received an infliximab 200 mg/infusion every 8 weeks and MTX 15 mg/week. Eight months after the start of this treatment about 10 skin lesions of up to 10 cm in diameter with erythema, scales, and pustules appeared on both legs and plantar area. Psoriasis pustulosa was clinically confirmed by a dermatologist. The psoriasis was pre-existing but had been asymptomatic for many years. A topical treatment was started and infliximab and MTX were continued. The psoriasis is continuing with moderate activity. Before infliximab, the patient had received etanercept 25 mg twice weekly without appearance of skin lesions.

Case 7

A 49 year old woman with RA was treated with etanercept 25 mg twice weekly. One month after the start of treatment she noticed about 10 erythematous and scaly skin lesions of up to 2 cm in diameter on both legs and arms. Psoriasis vulgaris was clinically diagnosed by a dermatologist. The psoriasis was pre-existing but had been almost asymptomatic for about 15 years. Etanercept was combined with MTX 15 mg/weekly, and additional topical treatment was started.

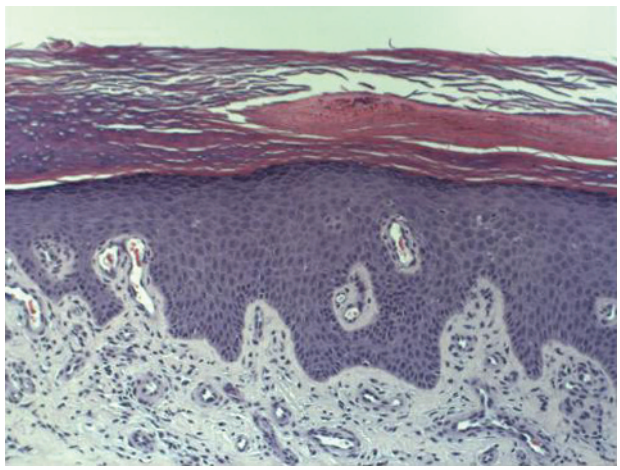

Figure 2 Histology of a patient (case 1) with psoriasis vulgaris.

Case 8

A 63 year old woman with RA was given etanercept 25 mg twice weekly. Two months after the start of treatment multiple erythematous scaly lesions appeared on the extremities and the trunk. Psoriasis vulgaris was clinically diagnosed by a dermatologist. Etanercept was continued. The psoriasis is stable with topical treatment.

Case 9

A 40 year old woman with RA received adalimumab 40 mg every other week in combination with MTX. Eleven months after the start of treatment, she noticed multiple pustules on both palms and soles and numerous scaly lesions on both ears and the hair line. Psoriasis vulgaris was clinically diagnosed by a dermatologist. Adalimumab was discontinued. Ciclosporin A was started instead, but treatment had to be changed to infliximab because ciclosporin A had insufficient effect on RA. The skin symptoms did not deteriorate with infliximab 200 mg/infusion every 8 weeks.

Table 1 summarises the treatment and the variety of psoriasis of these nine patients.

The diagnosis of RA was definite in each of our patients. Eight patients had a positive rheumatoid factor; four patients had tested positively for anti-cyclic citrullinated peptide antibodies. The clinical pattern and the radiographic lesions were characteristic for RA in all patients, including patient 6, who was rheumatoid factor negative and had pre-existing psoriasis pustulosa. The range of disease duration was 5–13 years, and at least two disease modifying antirheumatic drugs had failed in the treatment of all patients. HLA typing was performed in patients 1–4. All of them had HLA-DR4. Patient 4 additionally had HLA-Cw6, which is considered to be associated with psoriasis.[6] None of the commonly known trigger factors for psoriasis, such as infections, β adrenergic blockers, or lithium, were present in any of the patients before the eruption of psoriasis. Some patients had previously received antimalarial drugs, which did not evoke psoriasis. Five of the patients had pustulous symptoms of psoriasis, and in three of them psoriasis pustulosa was diagnosed.

DISCUSSION

As far as we know, this is the first demonstration of either a new onset or an exacerbation of psoriatic skin lesions during anti-TNFα treatment in a larger series patients with RA, eight of whom had been reported on in a EULAR abstract.[7] In an additional literature search, we found sporadic information on psoriasis and psoriasis-like symptoms in patients treated with TNFα antagonists for inflammatory bowel disease, ankylosing spondylitis, and RA.[2 8–12]

The co-incidence of RA and psoriasis of the skin is rare. In the German national data bank for rheumatological diseases (year 2002 – unpublished analysis of the Epidemiology Unit of the German Rheumatology Centre, Berlin), we found 26/11 428 (0.2%) patients with definite RA and 22/7734 (0.3%) patients with seropositive RA who simultaneously had psoriasis of the skin. As psoriatic inflammation is reduced by TNFα antagonists, some protection against a new incidence of psoriasis might have been expected.

However, the experience with TNFα blocking agents in the pustulous manifestation of psoriasis, which occurred in more than the half of our patients, is limited. Withdrawal or dose reduction of TNFα blocking agents led to improvement only in some patients, and was generally limited by the activity of the underlying RA. A change within the substance class reduced the severity of the symptoms in some patients, but

Table 1 Patient data, psoriasis diagnosis, type of TNFα antagonist, interval between last TNFα antagonist and onset/exacerbation of psoriasis

Case	RF	Anti-CCP	TNFα antagonists*	Latency‡ (months)	Psoriasis type	Histology	New onset	Family§
1	+	+	ADA†, ETA, INF, ETA	14	Vulgaris	Yes	Yes	No
2	+	+	ETA†	1	Pustulosa	Yes	Exacerbation	No
3	+	+	ETA, ADA†	(4 days)	Vulgaris	Yes	Yes	No
4	+	NA	INF†	2	Vulgaris	No	Exacerbation	Sister
5	+	+	ADA†	5	Pustulosa	Yes	Yes	Brother
6	Neg.	NA	ETA, INF†, ETA, ADA	8	Pustulosa	No	Exacerbation	No
7	+	NA	ETA†	1	Vulgaris	No	Exacerbation	No
8	+	NA	ETA†	2	Vulgaris	No	Yes	No
9	+	NA	ADA†, INF	11	Vulgaris	No	Yes	No

*In order of administration; †TNFα antagonist with onset or exacerbation of psoriasis; ‡latency: interval between first administration of the last TNFα antagonist and onset/exacerbation of psoriasis; §family member with psoriasis.
RF, rheumatoid factor, anti-CCP, anti-cyclic citrullinated peptide antibodies; ADA, adalimumab; ETA, etanercept; INF, infliximab.

which biological agent would prove to be less harmful could not be predicted.

A hypothetical explanation of appearance or deterioration of psoriasis might be the overall enhanced susceptibility to bacterial infections caused by TNFα inhibition, but no patient had a preceding bacterial infection. Hypothetically, the inhibition of TNFα influenced the manifestation of psoriasis skin lesions in our patients, which is in contrast with the reported therapeutic benefit of TNFα antagonists. A study of such patients with new onset or aggravation of psoriasis during TNFα blockage will be continued for further analysis of an underlying common pattern.

ACKNOWLEDGEMENTS

Supported by the Competence Network Systemic Inflammatory Rheumatic Diseases of the German Ministry of Education and Science

Authors' affiliations

S Kary, G-R Burmester, Department of Rheumatology and Clinical Immunology, Charité-University Medicine Berlin, Berlin, Germany
M Worm, H Audring, H Lee, W Sterry, Department of Dermatology and Allergy, Charité-University Medicine Berlin, Berlin, Germany
D Huscher, Epidemiology Unit, German Rheumatology Research Centre, Berlin, Germany
M Renelt, Rheumatology Clinic, Sendenhorst, Germany
H Sörensen, Rheumatologist, Berlin, Germany
E. Ständer, Rheumatology/Diabetes Unit, Hospital Schwerin, Germany
U Maaß, Rheumatology Centre, Suedstadt Klinikum, Rostock, Germany

Correspondence to: Professor G –R Burmester, Department of Rheumatology and Clinical Immunology, Charité-University Medicine Berlin, Schumannstr 20–21, 10117 Berlin, Germany; gerd.burmester@charite.de

Accepted 31 July 2005
Published Online First 8 September 2005

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